

## Relationship Between Plasma and Extracellular Fluid Volume Depletion and the Antihypertensive Effect of Chlorothiazide

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The importance of plasma and extracellular fluid volumes in the mechanism of the antihypertensive effect of chlorothiazide is disputed. The present investigation indicates that the lowering of blood pressure is accompanied by reductions in plasma and extracellular fluid volumes and in body weight. Furthermore, re-expansion of plasma volume with salt-free dextran reverses the antihypertensive effect. However, since gradual reaccumulation of extracellular fluid occurs during 1 year of continuous treatment, the *late* antihypertensive effects of chlorothiazide cannot be explained by the volume-depletion mechanism.

**T**HE discovery of the antihypertensive action of chlorothiazide<sup>1,2</sup> raised certain questions as to its mechanism of action. These questions included (1) whether the hypotensive response was caused by salt depletion or by some independent factor; (2) if produced by salt loss, by what mechanism it reduced blood pressure; (3) the factors that lead to increased reactivity to other antihypertensive agents; and (4) the reason for the moderate antihypertensive action of the drug when used alone in hypertensive patients and the absence of such activity in normotensive subjects.<sup>3,4</sup> Complete answers to these questions cannot yet be given. This report concerns an attempt to elucidate some of the factors involved.

### MATERIALS AND METHODS

Twenty male hypertensive patients with no symptoms or signs of congestive heart failure or edema were hospitalized and placed on a standard diet containing 1.5 Gm. of salt per day plus a supplement of 3 Gm. of salt in tablet form. This supplied a sodium intake of approximately 75 mEq. per day. Most of these patients were

under treatment with other antihypertensive agents (table 1), which were continued during the entire period of study. A 4-day period for acclimatization to the diet was instituted in order to obtain stabilization of body weight and electrolyte excretions as well as average basal blood pressure readings. Determinations of plasma and extracellular volumes, serum electrolyte concentrations, and serum bicarbonate were carried out on the morning of the fifth day. Each patient was then given 500 mg. of chlorothiazide twice daily, and the studies were repeated after a period of 3 to 8 (average 6) days.

In 11 patients carefully screened for reliability and conscientiousness in regard to taking their medications, studies were repeated at approximately 6-month intervals for a period of 12 months. Seven of these patients were hospitalized and placed on the controlled salt intake for 2 to 3 days prior to repeating the determinations, while the remaining 4 were hospitalized for 1 day only because of their inability to take time out from work. Thus, dietary intake of salt cannot be regarded as well controlled in the long-term studies. At approximately 6 months following initiation of treatment the determinations of plasma and extracellular volumes in 7 patients were repeated. Chlorothiazide therapy was then discontinued for 1 week, after which another series of determinations were carried out. The patients remained hospitalized throughout this latter period.

Plasma volume was determined in the fasting subject after one half hour of rest in the supine position with the Evans blue dye method of Gibson and Evans<sup>5</sup> adapted and modified for use in the Coleman spectrophotometer,<sup>6,7</sup> 3 specimens being

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TABLE 1.—Data Following Short-Term Therapy with Chlorothiazide.

Patient	Age	Other medication	Period of chlorothiazide treatment (days)	Blood pressure (mm. Hg)	Hematocrit (%)	Plasma volume (ml.)	Thiocyanate space (L.)	Body weight (Kg.)	Serum concentrations (mEq./L.)				CO <sub>2</sub>
									Na	Cl	K		
C.E.	46	—	8	—20/15	+2.1	—412	— .9	—2.0	—5	+5	—3		
J.Wr.	47	Reserpine	6	—26/16	+4.4	—501	— .9	— .9	—4	—7	+1		
N.M.	60	Reserpine	6	—17/6	+5.0	—783	—2.4	—3.3	—3	0	—6		
A.J.	46	Reserpine	7	—36/14	+ .5	—132	— .3	+1.3	+5	—10	—8		
J.Br.	43	Reserpine	7	—30/20	+3.0	—319	+ .1	+2.0	—1	0	—3		
J.Bu.	60	Reserpine	7	—15/10	+2.2	—568	—1.9	—2.7	+4	0	+1	0	
H.K.	40	Reserpine	8	—20/20	+1.7	—66	— .5	—1.2	—5	0	—4	1	
J.Z.	57	Reserpine	5	—10/0	+1.0	—296	—3.9	—2.2	+3	—10	—5		
A.N.	64	Reserpine	5	—20/5	— .4	—55	—1.4	— .7	+1	+1	—7		
N.B.	50	Reserpine	7	—15/15	+1.8	—460	—3.6	—4.0	—3	—2	—2		
J.We	66	Reserpine and Hydralazine	6	—40/18	+4.2	—265	—5.8	—4.6	0	—4	—2		
C.S.	36	Reserpine and Hydralazine	6	—14/20	+3.0	—741	—4.0	—1.4	—4	+9	—2		
T.H.	66	Reserpine and Mecamylamine	6	—40/25	+1.4	—598	—2.4	—3.0	—2	0	—3		
J.C.	47	Reserpine and Mecamylamine	4	—20/22	+ .5	—363	— .5	+ .2	—4	0	+2	—1.4	
C.P.	52	Reserpine and Mecamylamine	8	—50/30	+1.1	—177	—2.1	—2.2	—2	0	—3	—1	
M.P.	46	Reserpine and Mecamylamine	8	—25/10	+4.4	—222	—1.1	—1.0	—3	+6	—3		
G.B.	44	Reserpine and Chlorisondamine	8	—30/10	+4.2	—403	—2.0	—1.5	—3	—6	—7		
J.D.	47	Reserpine and Chlorisondamine	6	—10/10	+1.4	—39	—3.8	— .2	—1	—1	—2		
M.C.	42	Reserpine and Chlorisondamine	3	—10/25	+ .4	—172	+ .4	—2.3	—1	—4	—2		
S.E.	42	Reserpine, Hydralazine, Pentolinium	7	—25/15	+2.0	—596	—4.6	—5.4	+2	0	—6	+1	
Mean			6.4	—24/—15*	+2.2*	—358*	—2.1*	—1.8*	—1.3	—1.1	—3.2*	—1.5	
S. D.				11/7.5	4.9	223	1.75	1.84	2.9	4.8	2.74	1.8	

\**p* value less than .001.

used at 10, 15, and 20 minutes for determining dye dilution. The hematocrit value was determined from the average of 6 samples drawn during the various experimental procedures. Eighteen milliliters of 5 per cent sodium thiocyanate<sup>8</sup> were injected usually at the end of the plasma volume determinations and samples were drawn at 2 and 3 hours for determination of thiocyanate space according to the method of Crandall and Anderson<sup>8</sup> adapted to the Coleman spectrophotometer. Radiosulfate space was determined with S<sup>35</sup>-labeled sulfate by the method of Walser.<sup>9</sup> Sodium and potassium were determined with a flame

photometer. Serum chloride was determined by the method of Schales and Schales<sup>10</sup> and serum bicarbonate by a modification of the method of Van Slyke.<sup>11</sup>

All injectates were given in calibrated syringes; blood samples were drawn with minimal stasis. Blood pressure was determined by the auscultatory method before and after each experimental period. The patients were weighed prior to the procedures on a beam balance accurate to  $\pm 250$  Gm.

The cumulative negative balances of sodium, potassium, and chloride during the first 3 to 4 days of chlorothiazide treatment were estimated as follows: beginning 48 hours after institution of the diet 3 consecutive 24-hour collections of urine

\*Kindly supplied by Eli Lilly and Company, Indianapolis, Ind.

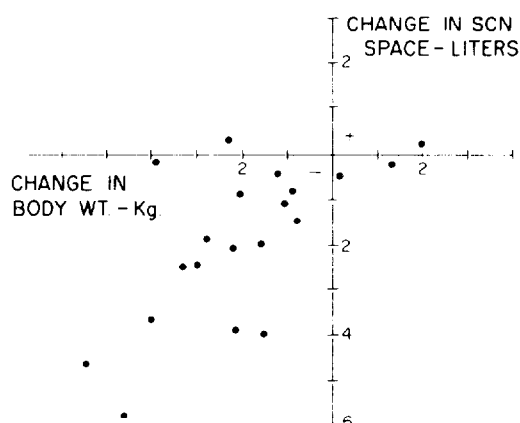


Fig. 1. Relationship between change in body weight and in thiocyanate space following short-term treatment with chlorothiazide.

were analyzed for total sodium, chloride, and potassium, and the average was taken as the control level of excretion. The cumulative elevations above this level during the first 3 to 4 days after chlorothiazide were then used to estimate electrolyte losses.

The effect of restoration of the plasma volume was determined in 7 patients who exhibited significant hypotensive responses to chlorothiazide. Each patient received 500 ml. of 6 per cent dextran in normal saline; and after several days the procedure was repeated with substitution of a similar volume of dextran in 5 per cent glucose in water. The infusion rate was approximately 25 ml. per minute. Blood pressure and heart rate were determined repeatedly before and throughout the procedure and blood for hematocrit determinations was drawn immediately preceding and following each infusion.

## RESULTS

### Acute Effects of Chlorothiazide

Following 3 to 8 (mean 6) days of chlorothiazide therapy the plasma volume showed some reduction in all of 20 nonedematous hypertensive patients (table 1). The loss of plasma volume averaged  $358 \pm 223$  ml. and varied in different patients from insignificant falls of less than 70 ml. to rather marked losses above 700 ml. The hematocrit reflected the plasma volume change in an approximate way by exhibiting slight to moderate elevation. However, there was no close quantitative relationship between hematocrit and plasma volume changes.

TABLE 2.—Losses after Chlorothiazide

Patient	Chlorothiazide treatment (days)	Urinary losses, cumulative negative balance (mEq.)			Change after chlorothiazide	
		Na	Cl	K	Thiocyanate space (L.)	Wt. (Kg.)
S. E.	3	224	392	209	—4.6	—5.4
J. Bu.	4	301	489	181	—1.9	—2.7
N. M.	4	290	560	168	—2.4	—3.3
J. Z.	3	162	135	154	—3.9	—2.2
J. T.	4	216	268	4	— .7	—2.2
E. W.	3	349	510	222	—3.4	—2.7
Average	3.5	257*	392*	156.3*	2.8*	3.0*
S. D.		68	163	71	1.4	1.2

\**p* value less than .005.

The thiocyanate space declined by more than 0.5 L. in all except 5 of the 20 cases (table 1). For the group as a whole the mean reduction was  $2.1 \pm 1.75$  L. Although the reductions of both plasma and available fluid spaces were significant ( $p < .001$ ), there was no consistent relationship between the degree of plasma volume and available fluid changes.

Body weight decreased in 16 of the 20 patients (mean  $1.8 \pm 1.84$  Kg.). The change in body weight was significant at the .001 level. There appeared to be a rough correlation between the extent of change in body weight and in thiocyanate space (fig. 1). The blood pressure fell in all patients, the average change being  $-24/15$  mm. Hg. The reduction occurred during the first 48 hours following institution of chlorothiazide. There was no quantitative correlation between the plasma volume and arterial pressure changes.

The cumulative losses of body electrolytes (cumulative negative balance) by the end of the third to fourth day of chlorothiazide treatment averaged  $257 \pm 68$  mEq. of sodium,  $392 \pm 163$  mEq. of chloride, and  $156 \pm 71$  mEq. of potassium in 6 patients studied (table 2). All of these patients exhibited significant reductions in body weight and thiocyanate space. The correlation between the extent of body weight reduction and electrolyte losses was poor in this small series. However, the accuracy of 24-hour urine collections cannot

TABLE 3.—*Effects of Intravenous Infusion of Six Per Cent Dextran in Saline and of Salt-free Dextran*

Patient	Chloro-thiazide treatment (mos.)	Control B.P. (mm.Hg)	After chloro-thiazide change mean B.P.* (%)	Following dextran infusion			
				In 5 per cent glucose change		In normal saline change	
				Mean B.P. (%)	Hematocrit (%)	Mean B.P. (%)	Hematocrit (%)
J.H.†	1.0	150/110	—16.2	+10.0	— 3.2	+ 9.0	— 5.8
J.C.†	.5	180/110	—22.9	+18.4	—11.4	+20.0	—12.0
C.S.‡	3.0	150/110	—13.0	+10.5	—12.1	+10.0	—12.8
R.C.‡	1.0	180/108	—30.4	+28.1	— 9.1	+23.7	—12.6
W.F.†	1.0	140/100	—11.3	+14.0	—13.6	+13.2	— 9.8
N.B.‡	1.0	145/95	—12.5	+19.0	— 8.8	+17.0	— 6.0
J.Z.†	2.0	142/96	—10.9	+ 8.4	— 5.0	—	—
Mean	1.4	155/104	—16.7§	+15.4§	— 9.0#	+15.4#	— 9.8#
S.D.			8.8	6.9	3.8	5.8	3.3

\*“Mean” blood pressure equals (systolic + diastolic)/2.

†On no other antihypertensive drugs.

‡Also receiving reserpine 0.25 mg. per day. C.S. also taking hydralazine 25 mg. t.i.d.

§*p* value less than .005.

#*p* value less than .001.

be regarded as completely reliable, even in hospitalized patients. The changes in the serum concentrations of sodium and chloride were insignificant, but there was a small but significant decrease in potassium (table 1). The serum bicarbonate determined in 4 patients showed essentially no change.

#### *Acute Restoration of Plasma Volume*

The effect of re-expansion of plasma volume on blood pressure was determined in 7 patients who had been under continuous treatment with chlorothiazide for periods ranging from 2 weeks to 3 months (mean 1.4 months). These patients had exhibited reductions of “mean” (systolic + diastolic)/2 blood pressure averaging  $17.0 \pm 9.0$  mm. Hg (table 3). The administration of 6 per cent dextran in isotonic saline in 6 of these patients resulted in an immediate elevation of blood pressure averaging  $15.0 \pm 6.0$  mm. Hg. The mean percentage fall in the hematocrit was  $9.8 \pm 3.3$  during the dextran infusion.

In order to determine whether sodium ion was important in the reversal of the antihypertensive effect the infusions were repeated after several days with 6 per cent

dextran in 5 per cent glucose in water. In 7 patients a significant elevation of blood pressure was observed ranging between 8 to 28 mm. Hg (mean  $+ 15.0 \pm 7.0$  mm. Hg, ( $p < .005$ )). The percentage fall of hematocrit averaged  $9.0 \pm 3.8$ .

#### *Effects of Long-Term Treatment with Chlorothiazide*

Whereas the reductions in plasma volume, thiocyanate space, and body weight were significant during short-term therapy with chlorothiazide, this was not the case following long-term treatment. In 11 patients when these parameters were measured at the end of 6 months, only the reduction in thiocyanate space remained significant (table 4). At the end of 1 year the change in thiocyanate space was no longer significant at the .05 level. Despite this trend, however, the blood pressure changes, although not as marked at the end of 1 year as in the early stages of therapy, still showed significant reductions.

In 9 patients after 1 to 3 months (average 1.8 months) the extracellular fluid volume was estimated by means of 2 indicators (table 5), thiocyanate and radiosulfate simultane-

TABLE 4.—*Changes Initially after Six and Twelve Months*

Patient	Plasma volume (ml.)			Blood pressure (mm. Hg)			Thiocyanate space (L.)			Body weight (Kg.)		
	1 wk.	6 mo.	12 mo.	1 wk.	6 mo.	12 mo.	1 wk.	6 mo.	12 mo.	1 wk.	6 mo.	12 mo.
J.We.	—265	— 22	+165	—40/—18	—30/—15	0/—8	—5.8	—3.9	— .7	—4.6	—1.1	—2.8
J.Wr.	—501	— 42	—212	—26/—16	—22/—20	— 7/0	— .9	—2.2	— .2	— .9	—6.0	—6.1
C.S.	—741	—201	—225	—14/—20	—20/—20	—30/—30	—4.0	—3.2	—1.2	—1.4	—8.0	—4.9
N.M.	—783	+ 74	+132	—17/—6	—20/—19	—35/—14	—2.4	—2.4	+1.2	—3.3	+ .2	—1.0
T.H.	—598	+110	—168	—40/—25	—30/—20	—20/—10	—2.4	— .4	— .7	—3.0	+7.7	+6.7
S.E.	—596	+ 58	— 19	—25/—15	—20/—20	—20/—22	—4.6	—4.7	+ .9	—5.4	—6.3	+5.7
J.C.	—363	—323	—402	—20/—22	—30/—20	30/—5	— .5	— .5	— .1	+ .2	+ .9	+4.9
J.Br.	—319	—248	—534	—30/—20	—28/—15	—10/0	+ .1	—2.1	—2.1	+2.0	+4.4	+1.9
J.Bu.	—568	—164	—336	—15/—10	—15/—20	—10/—15	—1.9	— .8	— .6	—2.7	+ .8	—1.4
C.P.	—177	— 51	— 51	—50/—30	—30/—20	—18/—20	—2.1	—1.1	—1.5	—2.2	—4.3	—7.0
H.K.	— 66	— 75	— 56	—20/—20	—20/—20	—20/—15	— .5	— .9	— .7	—1.2	— .1	+ .1
Mean	—452*	— 80	—155†	—27/18*	—24/19*	—18/13*	—2.3‡	—2.0‡	— .6	2.0‡	—1.0	— .4
S. D.	232	128	212	11.6/6.8	5.5/2	10.5/2.4	1.8	1.5	.9	2.1	4.6	4.7

\**p* value less than .001.†*p* value less than .05.‡*p* value less than .01.TABLE 5.—*Comparative Changes in Extracellular Fluid Volume before and after Chlorothiazide As Measured by Two Different Indicators*

Patient	Duration treatment (mos.)	Thiocyanate space (L.)			S <sup>35</sup> -labeled sulfate space (L.)			Thiocyanate change (%)	S <sup>35</sup> change (%)
		Control	After drug	Change	Control	After drug	Change		
J.W.	2	25.4	23.2	—2.2	19.9	15.7	—4.2	—11.5	—21
N.M.	3	19.8	17.4	—2.4	14.1	13.6	—0.5	—12	—4
A.J.	2	24.0	21.7	—2.3	17.7	17.3	— .4	—10	—2
T.H.	1	25.6	25.0	— .6	19.6	19.6	—0	—2	0
S.E.	1	24.5	21.1	—3.4	18.3	16.0	—2.3	—14	—13
J.Bu.	2.5	19.0	18.2	—1.8	14.4	13.2	—1.2	—11	—12
J.Br.	1	22.4	18.9	—3.5	18.6	15.8	—2.8	—16	—15
C.P.	1	18.9	16.3	—2.6	15.8	14.1	—1.7	—14	—11
H.K.	1	17.1	16.8	— .3	13.2	12.4	— .8	—2	—6
Mean	1.83	21.8	19.9	—2.1*	16.8	15.3	—1.5	—10.3*	—9.3†
S.D.				1.1			1.3	5	7.3

\**p* value less than .001.†*p* value less than .05.

ously, as an additional check on the validity of the change demonstrated with thiocyanate alone. Considerably more variation was observed with radiosulfate as the indicator. However, the average change for the group as a whole was similar with either thiocyanate or S<sup>35</sup>-labeled sulfate and the reduction in estimated extracellular space was still significant with either method.

Chlorothiazide was withdrawn for a 1-week

period in 8 patients after 3 to 7 (average 5.4) months of continuous treatment in order to evaluate the changes that might occur following discontinuation of long-term therapy (table 6). There was a prompt elevation of plasma volume averaging  $241 \pm 100$  ml., a rise in blood pressure (mean  $23/15 \pm 8/9$  mm. Hg), and a gain in body weight averaging  $1.6 \pm 1.3$  Kg. All these changes were significant at the .01 level or less. The in-

TABLE 6.—*Changes Following Discontinuation of Chlorothiazide*

Patient	Duration treatment (mos.)	Plasma volume (ml.)			Blood pressure (mm. Hg)			Thiocyanate space (L.)			Body weight (Kg.)		
		After chlor.	Repeat control	Gain or loss	After chlor.	Repeat control	Gain or loss	After chlor.	Repeat control	Gain or loss	After chlor.	Repeat control	Gain or loss
J.We.	4	3720	3827	+107	170/100	200/120	+30/20	23.	26.9	+2.1	85.3	85.3	0
J.Wr.	7	3717	4106	+389	151/103	180/130	+29/27	26.4	25.4	-1.0	103.3	104	+ .7
C.S.	7	3537	3871	+234	128/87	150/110	+22/23	19.6	20.7	+1.1	73.0	74.3	+1.3
T.H.	7	3943	4152	+209	153/100	160/110	+ 7/10	24.7	25.6	+ .9	92	94.3	+2.3
S.E.	7	3183	3525	+342	160/110	180/125	+20/15	24.2	25.6	+1.4	71.5	72.7	+1.2
J.C.	5	3340	3663	+323	170/100	200/110	+30/10	22.8	23.0	+ .2	95.4	99.5	+4.1
J.Br.	3	3200	3350	+150	140/100	165/100	+25/0	18.9	22.4	+3.5	80.3	83.0	+2.7
H.K.	3	2931	3106	+175	130/90	150/110	+20/20	16.4	17.2	+ .8	70	70.7	+ .7
Average	5.4	3446	3700	+241*	150/99	173/144	+23*/15†	21.5	23.4	+1.1	83.8	85.2	+1.6†
S.D.				100.4			7.8/8.8			1.4			1.3

\**p* value less than .001.†*p* value less than .05.

crease in thiocyanate space averaged  $1.1 \pm 1.4$  L. The latter change was of questionable significance ( $p < .06$ ).

As compared to pretreatment values it was of interest that following discontinuation of the drug plasma volume increased  $120 \pm 18$  ml. and thiocyanate space rose to  $0.5 \pm 0.3$  L. above the original, untreated level. These slight overshoots were not accompanied by parallel behavior of the blood pressure, the latter remaining  $-4/6 \pm 7/7$  mm. Hg below the pretreatment level.

The changes in serum electrolyte concentrations and in serum bicarbonate were determined after 1 year of chlorothiazide treatment in 11 patients (table 7). Serum sodium concentrations were essentially unchanged. Serum chloride levels decreased slightly in most patients but increased slightly in 2, the average change being  $4.4 \pm 6.8$  mEq. There was a significant decline in serum potassium concentrations. The mean reduction was  $1.1 \pm 0.6$  mEq. ( $p < .001$ ). The serum bicarbonate remained unchanged.

#### DISCUSSION

In the present observations the reduction of blood pressure paralleled the saluresis and did not precede or follow it. The saluretic effect was essentially complete in 48 hours. The question arises as to the source of the

sodium depletion, specifically as to whether it represented reductions in intracellular stores or came from the extracellular fluid. The maintenance of normal serum sodium levels indicated that the drug did not extract sodium from the extracellular water. However, the extent of the depletion of extracellular fluid volume indicated that the majority if not all of the sodium removed could be accounted for by an excretion of isotonic, extracellular fluid. This is in keeping with the observations on other saluretic agents such as mercurials, which produce primarily a reduction of extracellular fluid volume.<sup>12</sup>

Since the plasma volume is in equilibrium with the interstitial fluids, it also shared in the general reduction of extracellular fluid space. However, the relationship between change in extracellular and plasma volumes is only approximate.<sup>13</sup> Because of the failure to find any evidence for significant cellular losses of sodium, the question arose whether the antihypertensive effect was related simply to the decrease in total circulating blood volume and to a reduction in tissue pressure secondary to the extracellular fluid loss. Such an interpretation is supported by the observation of Crosley and his associates<sup>14</sup> that right heart pressures and cardiac output are reduced by chlorothiazide. Preliminary

TABLE 7.—*Changes Following One Year of Treatment with Chlorothiazide*

Patient	Change in mEq.			
	Na	Cl	K	CO <sub>2</sub>
J.We.	—3	—4	— .8	—1.
J.Wr.	—1	—12	— .3	—1.6
C.S.	0	—9	— .6	—2.0
N.M.	—1	—9	— .6	+4.8
T.H.	+2	—11	—1.1	+3.1
S.E.	0	—8	—1.5	+3.2
J.C.	—4	—1	— .4	+2.0
J.Bu.	—5	+9	—1.2	—3.0
J.Br.	—1	—3	— .4	—1.0
C.P.	—4	+5	—2.1	—4.0
H.K.	0	—5	—1.0	+1.0
Mean	—1.5	—4.4*	— .95†	+ .2
S.D.	2.5	6.8	.6	2.9

\**p* value less than .05.†*p* value less than .001.

results in this laboratory tend to confirm these observations. Dustan and her co-workers<sup>15</sup> also found a reduction in cardiac output following chlorothiazide.

If the antihypertensive effects of chlorothiazide were due to a change in intracellular sodium concentration producing a decrease either in arteriolar tone or a dehydration of "waterlogged" arterioles,<sup>16</sup> the hemodynamic effects should be reflected in a reduction of total peripheral resistance rather than a fall in cardiac filling pressures and output. The latter findings, however, are readily explained by the decreases in plasma and extracellular fluid volumes. It is of interest that the normotensive individual compensates so that the basal blood pressure is not lowered, whereas this compensation seems to be deficient in hypertensive patients.<sup>3,4</sup> Whether such failure of homeostasis is due to a decreased responsiveness of the baroreceptors or to other factors cannot be determined on the basis of present evidence.

The importance of the plasma volume change in the mechanism of the antihypertensive effect was indicated by the fact that restoration of plasma volume either with or without any replenishment of sodium restored the blood pressure to essentially pre-

treatment levels. The lack of a quantitative relationship between the decrease in plasma volume and the fall of blood pressure can be explained on the basis of variations in the activity of compensatory mechanisms including the baroreceptor reflexes, and intrinsic vascular distensibility in different individuals. This variability was further enhanced by the fact that some of the patients were taking ganglion-blocking drugs and others were not.

These conclusions on the importance of oligemia in the mechanism of the antihypertensive action of chlorothiazide confirm our initial findings<sup>3</sup> and are similar to those expressed by Dustan, Tapia, and associates.<sup>15, 17</sup> They propose that the oligemia enhances vasomotor "tone" which in turn makes the patient more responsive to ganglion-blocking agents. However, the observation that the hypertensive patient often shows some reduction of blood pressure with chlorothiazide alone whereas the normotensive subject does not<sup>3,4</sup> suggests that the compensatory mechanisms for plasma volume depletion often are inadequate in hypertension. Also, the decreased responsiveness to norepinephrine following chlorothiazide<sup>18, 19</sup> in normotensive subjects is not readily explained on the basis of increased vasomotor tone alone, and suggests that reactivity is dependent to some extent on the degree of filling of the vascular system.

The failure to observe a significant reduction of plasma volume after 6 to 12 months of treatment reflects either tolerance to the saluretic effects of the drug or the establishment of compensatory mechanisms for restoration of homeostasis. Compensatory mechanisms become active after the first 48 hours of treatment when the output of sodium comes back into balance with the intake. However, in the first month of treatment the depletion achieved during the initial saluresis is maintained and only gradually, thereafter, is the plasma volume deficit made up.

Other investigators have postulated that chlorothiazide may have antihypertensive effects additional to its saluretic action.<sup>4</sup> This

is based on the observation that the blood pressure remains below pretreatment levels after the body weight has been restored. It should be pointed out, however, that disappearance of acute drug effects without return to pretreatment levels of blood pressure is not unique for chlorothiazide. For example, the acute hemodynamic effects of hydralazine, characterized by tachycardia and palpitation reflecting an increase in cardiac output, generally disappear with long-term treatment. Similarly, the manifestations of ganglionic blockade such as impaired visual accommodation, dry mouth, and postural hypotension often diminish with long-continued therapy even though basal arterial pressure remains below the pretreatment level. The observations of Perry and Schroeder<sup>20</sup> indicate that vigorous treatment to obtain a continuous and prolonged reduction of arterial pressure, often modifies the severity of the hypertension, so that less intensive or no further treatment is required. Thus, after long-term therapy many factors, such as tolerance, compensatory reactions, and modification of the basal level of blood pressure, come into play to obscure the initial relationship between drug action and antihypertensive effect. It does not seem possible to draw valid conclusions concerning the antihypertensive activity of a drug at this late stage, especially if the effects of drug withdrawal are not determined.

#### SUMMARY AND CONCLUSIONS

Plasma and extracellular fluid volumes, serum electrolyte concentrations, arterial pressure, body weight, and electrolyte excretions were determined in hypertensive patients treated with chlorothiazide.

Plasma and extracellular fluid volumes decreased promptly during the early phases of treatment. This was accompanied by a reduction of arterial pressure and body weight. Sodium losses could be accounted for on the basis of extracellular fluid volume depletion. Restoration of plasma volume either with or without partial replenishment of sodium reversed the antihypertensive effect of chloro-

thiazide. Withdrawal of chlorothiazide after 3 to 7 months of treatment was followed by an elevation of plasma volume usually to levels slightly above the control. Blood pressure rose to levels slightly below the control.

Significant reductions of plasma volume and body weight were not found after 6 months and of extracellular fluid volume after 12 months of therapy even though the blood pressure remained reduced. However, the latter may not be a valid criterion of drug activity following long-term modification of the blood pressure level. The only significant change in serum electrolyte concentration was a reduction in serum potassium. Serum bicarbonate levels were not altered.

On the basis of this and other evidence discussed it is suggested that the decrease in plasma volume is an important factor producing the initial antihypertensive effect. Reduction in tissue pressure secondary to extracellular fluid volume depletion also could contribute to this response.

#### SUMMARIO IN INTERLINGUA

Le volumines del plasma e del liquido extracellular, le concentrationes del electrolytos in le sero, le tension arterial, le peso corporee, e le excretion de electrolytos esseva determinate in patientes hypertensive sub tractamento con chlorothiazido.

Le volumines de plasma e de liquido extracellular descendeva promptemente durante le phases initial del tractamento. Isto esseva accompagnate per un reduction del tension arterial e del peso corporee. Le perditas de natrium esseva explicabile super le base del depletion del volumine de liquido extracellular. Le restauration del plasma, tanto con como etiam sin le restitution partial de natrium revertava le effecto antihypertensive de chlorothiazide. Le privation de chlorothiazido post 3 a 7 menses de tractamento esseva sequite per un elevation del volumine del plasma, usualmente usque a nivellos levemente supra le nivellos de controlo. Le tension del sanguine montava usque a nivellos levemente infra le nivellos de controlo.



Significative reductiones del volumine del plasma e del peso corporee non esseva constatate post 6 menses de therapia, e similimente nulle significative reductiones del volumine del liquido extracellular esseva constatate post 12 menses de therapia ben que le tension de sanguine remaneva reducite. Tamen, iste ultime facto es possibilmente invalide come criterio del activitate del droga post un prolongate modification del nivello del tension de sanguine. Le sol significative alteration in le concentration de electrolytos in le sero esseva un reduction del contento de kalium. Le nivellos de bicarbonato in le sero non esseva alterate.

Super le base de iste e altere observationes discutite in le presente reporto, le these es formulate que le reduction del volumine del plasma es un importante factor in le production del effecto antihypertensive initial. Le reduction del pression del histos que seque le depletion del volumine de liquido extracellular es etiam possibilmente un contributor a ille responsa.

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